Correspondence

Journal of Medical Genetics (1973). **10**, 396–399.

Alport's Syndrome

Sir,

In your issue of March 1973 I read with great interest a paper 'Segregation ratios in Alport's syndrome' by E. MacNeill and R. F. Shaw. This paper considered pooled data from 35 published pedigrees and drew the conclusion that these data do not support the hypotheses of dominant partially sex-linked inheritance, sex-limited dominant autosomal inheritance, or autosomal dominant inheritance with distorted segregation. While this may well be true, it should be noted that the 35 pedigrees are in several ways heterogeneous and hence pooling them is a questionable procedure.

1. Data from a paper by McConville, West, and McAdams (1966) are included. These authors state 'The familial type [of benign haematuria] was distinguished from Alport's syndrome . . . by lack of nephritis in the family, a benign clinical course, and renal biopsy. The mode of inheritance appeared to be autosomal dominant.' Their data should be excluded.

2. Even omitting McConville *et al*'s nine pedigrees, the data of McNeill and Shaw's Table I are not homogeneous. Considering only the seven pedigrees of Cassady *et al* (1965) (which included five previously published by Cohen, Cassady, and Hanna [1961]) we can look at the sex ratio in the offspring of affected males and females, as set out here in Table I.

Testing the data of Table I for homogeneity,

$$\chi^2_{18} = 40{\cdot}7805 \text{ with } 0{\cdot}01 > p > 0{\cdot}001.$$

TABLE I

SEX RATIO IN CHILDREN OF AFFECTED PARENTS IN FIVE PEDIGREES OF COHEN *et al* (1961) AND TWO OF CASSADY *et al* (1965)

Pedigree	Offspring of Affected Males		Offspring of Affected Females		Totals
	Males	Females	Males	Females	
1	3	7	30	27	67
2	1	3	13	10	27
3	6	7	9	13	35
4	40	27	38	50	155
5	30	29	37	31	127
6	8	10	9	12	39
7	6	4	6	8	24
Totals	94	87	142	151	474

Hence, these data are heterogeneous among pedigrees with respect to at least one of the comparisons implicit in MacNeill and Shaw's Table I and so cannot validly be pooled.

3. From the same two papers, it is possible to make the following comparison:

	Males			Females			Totals
	Deafness Only	Renal Disease Only	Deafness and Renal Disease	Deafness Only	Renal Disease Only	Deafness and Renal Disease	
Cohen *et al* (1961)	5	51	31	2	92	24	205
Cassady *et al* (1965)	9	24	26	21	18	20	118
Totals	14	75	57	23	110	44	323

These groups are not homogeneous ($\chi^2_5 = 61{\cdot}0$, $p < 0{\cdot}001$) but the high frequency of deaf males and females may be contrasted with other data as in Table II.

As not all the authors cited in Table II tested all possible members of each pedigree for deafness (eg, Patton

TABLE II

NUMBERS OF INDIVIDUALS MANIFESTING DEAFNESS ONLY AS AGAINST RENAL DISEASE ONLY OR DEAFNESS PLUS RENAL DISEASE IN 10 SURVEYS

Source	Males		Females	
	Deaf Only	Other Affected	Deaf Only	Other Affected
Cohen *et al* (1961) (5 pedigrees)	5	82	2	116
Cassady *et al* (1965) (2 pedigrees)	9	50	21	38
Shaw and Glover (1961)	0	10	0	23
Patton (1970)	0	8	2	7
Mulrow *et al* (1963)	0	16	0	13
Antonovych *et al* (1969)	0	4	0	7
Perkoff *et al* (1958)	6	15	0	23
Wasserman *et al* (1965) (4 pedigrees)	1	10	1	13
Sturtz and Burke (1958) (2 pedigrees)	4	13	6	17
Opitz (1962)	0	5	0	8

TABLE III

SIBSHIP SIZE IN THE PEDIGREES OF COHEN *et al* (1961) AND CASSADY *et al* (1965)

	Offspring of Normal Females		*Offspring of Normal Males*	
	(a) All normal	(b) Some affected	(c) All normal	(d) Some affected
Mean ± SE	2·33 ± 0·18	4·17 ± 0·67	2·32 ± 0·20	5·00 ± 0·73
No. of sibships	43	12	38	14
	Offspring of Affected Females		*Offspring of Affected Males*	
	(e) All normal	(f) Some affected	(g) All normal	(h) Some affected
Mean ± SE	2·08 ± 0·26	4·40 ± 0·33	2·62 ± 0·40	3·25 ± 0·24
No. of sibships	13	78	12	59

[1970] did not) and because some appear to have different proportions from others of very young affected individuals (who would not be old enough to manifest progressive hearing loss), it is not appropriate to perform a further test, but nonetheless there is again evidence of heterogeneity among families.

4. MacNeill and Shaw stated that one of their purposes was to 'investigate reproductive fitness of the abnormal genotype' and for this purpose they needed 'pedigrees uniformly suitable for comparison with US census data'. As the pedigrees are heterogeneous, pooling for this purpose may be inappropriate, but interesting results are obtainable from the pedigrees of Cohen *et al* (1961) and Cassady *et al* (1965).

If the sibships in the pedigrees are classified thus:

Mothers *or* fathers: normal *or* abnormal

Offspring: all normal *or* some abnormal

then Table III can be derived (having first shown that sibship sizes do not differ between pedigrees, unlike sex ratio and expression as discussed in 1 and 2 above; these analyses are not presented for reasons of brevity).

In Table III, the following sibship size differences are significant at the 0·1% level:

(a) and (b)

(c) and (d)

The following sibship size difference is significant at the 1% level:

(f) and (h)

The following sibship size differences are significant at the 5% level:

(e) and (f)

(g) and (h)

The following sibship size differences are not significant at the 5% level:

(a) and (c)

(b) and (d)

(e) and (g)

The difference between (g) and (h) might be expected if there is differential viability for the two sexes during the reproductive period, but the generally smaller all normal families suggest some kind of bias in ascertainment or sampling, so that these pedigree data may be unsuitable for examination of fertility differences. I have discussed this point elsewhere (Mayo, 1969/70).

As noted above, the data may well not fit any of the three suggested modes of inheritance; but if so, this may be because not all cases of Alport's syndrome have the same genetical component in their aetiology. The analyses presented here tend to lend support to the existence of such genetical heterogeneity.

Yours, etc,

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Sir,

Mr Mayo is probably right when he says that MacNeill and I should not have included the pedigrees of McConville, West, and McAdams, but there is no certainty in such matters at present, because the current definition of Alport's syndrome may be too restrictive or too inclusive. In any case, the general thesis that one should not pool pedigrees with different characteristics is not persuasive. What MacNeill and I set out to do was to pool a number of pedigrees, admittedly somewhat different among themselves, to see whether abnormal ratios are observable in the totals, and whether they fit the explanation of Shaw and Glover. I cannot see the harm in pooling pedigrees for this purpose. In biological studies if we waited until our materials were free of unexplained variation, we would never be able to begin.

Mr Mayo has shown by statistical test that pedigrees for the syndrome are heterogeneous. I think that is true. The pedigrees analysed by Glover and myself showed differences in some of their ratios. I know of an unpublished pedigree in which deafness is absent, but the other manifestations, including abnormal segregation, are present. It does, indeed, appear that Alport's syndrome is quite variable, both among members of a family and among pedigrees. It has never seemed to me urgent to demonstrate this variability statistically, as I could not see that such a demonstration would show anything very illuminating. Probably pedigrees of all hereditary diseases are heterogeneous for reasons of genetic modification and environmental influences. Alport's syndrome is clearly more variable than many. Hence statistical proof of heterogeneity among the pedigrees does not constitute an advance in knowledge unless some pattern can be shown. Is the variation continuous? bimodal? dichotonous? (Professor Clarke Fraser has suggested to me that there may be two kinds of Alport's syndrome with and without the abnormal ratios.) Are there correlations with climate or diet, or with ethnic origin? Are severity of symptoms and degree of abnormal segregation correlated? I am inclined to suppose that the cause of the disease is a chromosomal rearrangement and that in different families the break points are different or different linked modifiers are at work. But that is only speculation. Dietary effects, observed by Alport, remain to be followed up.

Mayo's finding of larger family size when a parent is affected strikes me as surprising and interesting. It is not entirely clear why he thinks it is an artefact, but in any event, it neither supports nor refutes anything MacNeill and I have claimed. We did not calculate any fitness values. The phrase about our interest in reproductive fitness which Mayo quotes is taken out of a sentence which says that one of our *initial* purposes was to investigate this subject. But in fact we abandoned that plan. The plan was mentioned in the paper by way of explaining why only pedigrees from the US were analysed.

Incidentally, I still think the Shaw and Glover explanation of this disease is by far the best available, and I regret now that MacNeill and I acquiesced at the instance of one of the assessors and toned down the conclusions given in the summary. The Shaw and Glover hypothesis is still in the running, but our summary appears to say that we favour no hypothesis. It seems to me better science to put forward strongly the best hypothesis available and see if other workers are stimulated to disprove it or to find a more appealing one. The alternative may be a rather dull and self-congratulatory consensus that nothing is known and nothing can be.

Yours, etc,
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The Crouzon Syndrome

Sir,

We strongly object to the diagnosis of craniofacial dysostosis (Crouzon syndrome) in the two sibs reported recently by Juberg and Chambers (1973). Despite the shallow orbits present in both patients, the lack of proptosis rules out the Crouzon syndrome, which is characterized *minimally* by craniosynostosis, midface hypoplasia, and shallow orbits with secondary proptosis (Cohen, 1973). Occasionally, craniosynostosis may even be absent, as in several affected family members reported by Shiller (1959).

The Crouzon syndrome follows an autosomal dominant mode of transmission with complete penetrance and variable expressivity. The possibility of genetic heterogeneity should always be kept in mind. However, that an autosomal recessive form of the Crouzon syndrome exists still remains to be shown.

The patients reported by Juberg and Chambers (1973) represent an isolated form of craniosynostosis, consistent with autosomal recessive inheritance. One of us (M.M.C.) has also observed several instances of affected sibs with isolated craniosynostosis.

Yours, etc,
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